Remarks

Claims 4-6, 8, and 20, 21, 23-25, 27-29, and 31-41 are pending. A copy of the pending claims is attached as an appendix. Claims 24 and 25 have been allowed. Applicants appreciate the withdrawal of the rejection of claims 31 and 37 under 35 U.S.C. § 102(b) over Broze et al., "Purification of Human Brain Tissue Factor", *J. Biol. Chem.* 260(20) 10917-20 (1985). Applicants also appreciate the withdrawal of the rejection of claims 24 and 25 under 35 U.S.C. § 112, first paragraph.

Claim 4 is drawn to purified human tissue factor protein, having at least the first 219 amino acids of tissue factor, with or without a substituted glycosylated amino acid. Claim 20 is drawn to a soluble tissue factor protein expressed from a nucleotide molecule encoding the amino acid sequence of Figure 2 from amino acid one to an amino acid residue between amino acid residues 219 and amino acid residue 263. Claim 31 is drawn to recombinant human tissue factor proteins expressed from a nucleotide sequence encoding an amino acid sequence which includes amino acids 1 to 219 as disclosed in Figure 2. Claim 41 is drawn to recombinant human tissue factor proteins which includes amino acids 1 to 219 as disclosed in Figure 2.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 4-6, 8, 20, 21, 23-25, 27-29, 31-36, and 38-41 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification, as originally filed, does not reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. This rejection is respectfully traversed.

The main arguments presented by the Examiner revolve around the lack of specific reference to specific tissue factor variants within the region spanning amino acids 219-263. The Examiner and Applicant are in agreement that:

1. The specific embodiments of a claimed genus do not need to specifically be described (see page 3 of the Office Action mailed January 14, 1999).
2. The standard for description as outlined in *Vas Cath* requires that the specification describe the invention with reasonable clarity so that one of ordinary skill in the art would understand that the inventor was in possession of the invention at the time of filing the application (see page 4 of the Office Action dated January 14, 1999).

Given the common ground between the Examiner's position and their own, Applicants submit that once the Examiner fully appreciates the position outlined by the Konigsberg Declaration, one of skill in the art, the Examiner will agree that the present application and priority applications clearly describe the claimed subject matter at the level required by the Federal Circuit.

Residues 1-219 and 220-242/43 are adequately described by the specification.

The Konigsberg Declaration shows that one of ordinary skill in the art would find the claimed subject matter adequately described.

The Konigsberg Declaration indicates that one of ordinary skill in the art at the time the application was filed would know that the transmembrane domain would bridge the extracellular regions and the cytoplasmic regions. Furthermore, Dr. Konigsberg goes on to state that those of skill in the art understood that the "extracellular domain could be used separately from both the transmembrane region and the cytoplasmic region." (Konigsberg Declaration at 3). Dr. Konigsberg sums up the knowledge of one of ordinary skill in the art at the time of the priority application by saying,

> "It is clear, those of skill in the art at the time would have understood, that deletion of the transmembrane region **is equivalent** to deletion of both the transmembrane region and cytoplasmic region, since the cytoplasmic domain serves no purpose in the absence of the transmembrane domain."

(Konigsberg Declaration at 4, emphasis added).

The Konigsberg Declaration stands for the proposition that once one of ordinary skill in the art understood that the transmembrane region existed and the cytoplasmic region was unnecessary, one of ordinary skill in the art would interpret a deletion of the transmembrane region to simply refer to a deletion of the *carboxy terminal portion* of the protein, from the transmembrane region through the amino terminus of the protein, i.e. amino acid 220. In other words, one of ordinary skill in the art, understanding how and why protein deletion variants are

made, would understand that the easiest way to delete the transmembrane region would be to simply insert a stop code into the DNA. The expressed protein would then terminate prior to the transmembrane domain.

The Examiner believes that the specification requires that the protein be cut into three pieces, the extra cellular region, the transmembrane region, and the cytoplasmic region, and then splice the cytoplasmic region back together with the extracellular region. This is quite simply not the reading that one of ordinary skill in the art would apply to the phrase "deletion of the transmembrane region," as discussed by Dr. Konigsberg. At most, one of ordinary skill in the art would recognize this as one way of deleting the transmembrane region, but would also recognize that this is not the preferred way because of the added difficulty in making this specific variant without any requisite benefit. As Dr. Konigsberg has stated, the preferred way, readily understood as being described in the specification by one of ordinary skill in the art, would be to delete the cytoplasmic portion of the protein along with the transmembrane domain because the cytoplasmic region was not functionally required.

The Examiner has taken the position that the statement "a major *class* of substitutional or deletional variants *are those involving* the transmembrane, i.e. hydrophobic or lipophilic, region of tissue factor protein" (page 15 of the specification, emphasis added) does not convey to one of ordinary skill in the art that applicants were in possession of "other deletion variants at the time the invention was made." The word "involving" would not be interpreted by one of ordinary skill in the art as "only" the transmembrane domain, as indicated by Dr. Konigsberg. This

sentence clearly conveys that applicants contemplated deletion variants which include both the deletion of the transmembrane region and deletion of other amino acids.

The Examiner consistently refers to what one of ordinary skill in the art would understand from the application, but apparently refuses to acknowledge the expert opinion of what one of ordinary skill in the would know. The Konigsberg Declaration is evidence made of record, and the arguments put forth by the Examiner to rebut the Konigsberg Declaration are not supported by evidence made of record. Evidence made of record can not be ignored or rebutted absent evidence to the contrary.

A protein variant described by reference to amino acid 219 is fully described in the application.

Claims 4-6, 8, 20-21, 23, 27-29, 31-36 and 38-41 are drawn to molecules that include at least the first 219 amino acid residues of human tissue factor. The first 219 amino acids are fully described in the application. As pointed out in the application and reiterated in the Konigsberg Declaration, human tissue factor consists of three domains. The middle domain is the transmembrane domain and consists of residues 220-242/243 as described in the application. As stated in the Konigsberg Declaration, one of ordinary skill in the art given this information would readily realize that there would be an amino terminal portion consisting of residues 1-219 and a carboxy terminal portion consisting of residues 243/244 to 263. Thus, a person of ordinary skill in the art would know that a fragment of amino acids 1-219 precedes the transmembrane domain region and that residue 243/244 follows the transmembrane domain region.

Again, the only rationale provided in the rejection in support of this conclusion is that tissue factor protein from amino acid 1 to 219 is not *explicitly* described.[1] However, as noted above and as acknowledged in the Office Action, such literal description is not required to satisfy the description requirement. All that is required is that the application reasonably convey to those of skill in the art that applicants were in possession of the claimed subject matter. The mere conclusory statement in the rejection does not outweigh the expert analysis and testimony to the contrary. Applicants submit that the un-rebutted evidence of record indicates that the application does convey that applicants were in possession of tissue factor protein from amino acid 1 to 219 at the time the application was filed.

Since the un-rebutted evidence of record indicates that the specification conveys to those of skill in the art that applicants were in possession of a tissue factor protein lacking the C-terminal region beyond amino acid 219, a claim to a tissue factor protein comprising amino acids 1 to 219 is supported by the specification within the meaning of the first paragraph of 35 U.S.C. § 112. In this regard, applicants note that there is no basis in the description requirement of 35 U.S.C. § 112 for limiting applicants to a tissue factor "consisting of" amino acids 1 to 219. Where a composition is adequately described in an application, applicants are entitled to claim the composition using open, "comprising" language. All aspects of the protein are known and adequately described in the application. The sequence of the region 1 to 219 is known, the

[1]Applicants also dispute that the application fails to provide an explicit description (see discussion of Figure 5 above).

sequence of the transmembrane domain is known, and the sequence of the carboxy terminus region is known. The function of the various regions is known. There is absolutely no legal basis for restricting the applicants to the "consisting" language.

The hydropathy profile of Figure 5 does convey to one of ordinary skill in the art, in conjunction with the specification, that deletion mutants could be made, and where appropriate deletions should be made.

In summary, the subject matter of the claims is fully described and allowance of claims 20, 21, 23, 24, 25, 27, 28, 29, and 31-41, is earnestly solicited.

Respectfully submitted,

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I hereby certify that this Amendment and Response to Office Action, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Teresa R. Spratt

Date: April 28, 1999